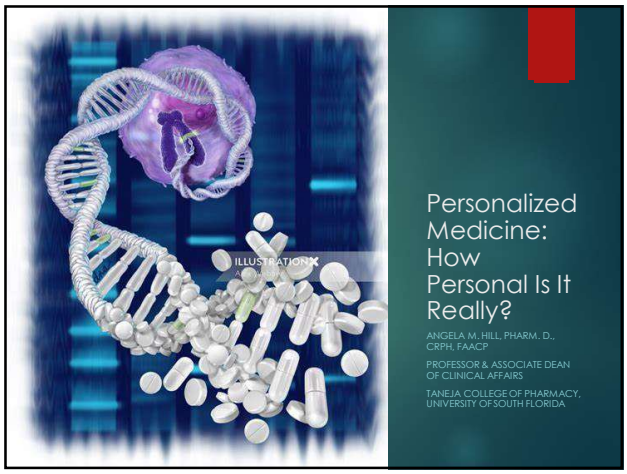


Personalized Medicine: How Personal Is It Really?

ANGELA M. HILL, PHARM. D., CRPH, FAACP

PROFESSOR & ASSOCIATE DEAN OF CLINICAL AFFAIRS

TANEJA COLLEGE OF PHARMACY, UNIVERSITY OF SOUTH FLORIDA

1

Disclosure

I HAVE NOTHING TO DISCLOSE.

2

3

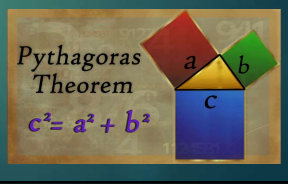
Learning Objectives:

1. Discuss key therapeutics areas where personalized medicine is being applied.
2. Discuss opportunities for pharmacy practice in pharmacogenomics.
3. Describe implications of pharmacogenonic applications with select medications.

4

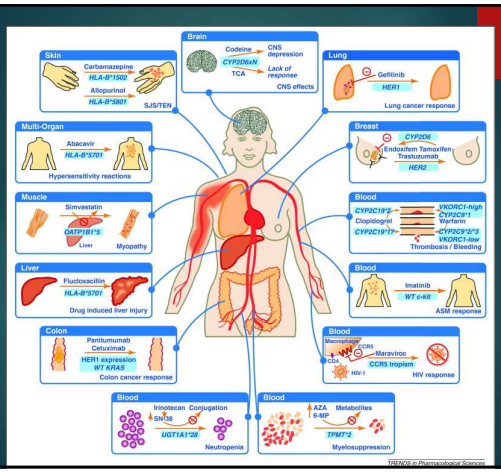
Pythagoras (570 BC to 495 BC)

- Favism
- Hemolytic anemia
- G6PD Deficiency



https://bit.ly/44qnSBe
https://www.nejm.org/doi/10.1056/NEJMra1708111

5



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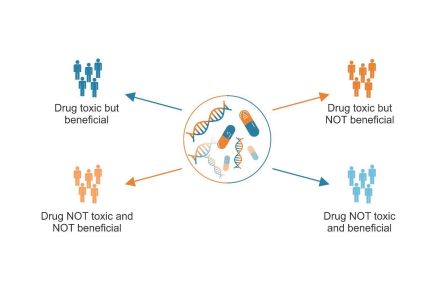
Value of Pharmacogenomics



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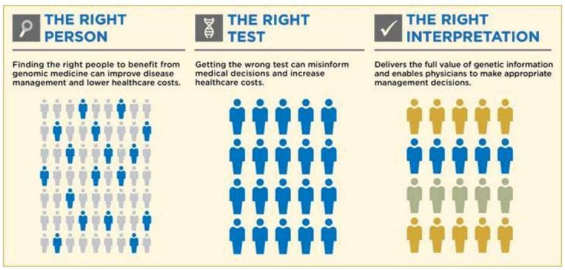
Opportunities for Pharmacogenetic Testing in General

- Drug treatments for which efficacy responses are unpredictable.
- Drugs that cause serious adverse events resulting in patient harm.
- Serious and non-serious adverse drug events or complications that cause drug failure or substantially delay successful treatment of disease.
- Drug treatments that have marked efficacy in small subpopulations, but dramatically less efficacy in larger populations with a given disease.

8

Benefits of Pharmacogenomics



9

Clinical Utility of Pharmacogenomics

- CPIC Guidelines
- PharmGKB
- GWAS Studies

10

CPIC Guidelines

- CPIC Guidelines use evidence-based data to help clinicians determine how available genetic tests can be useful in medication selection
  - As of June 2019, there were 132 pharmacogenomic dosing guidelines for 99 drugs and over 309 medications have language in their package inserts with pharmacogenomic information

https://cpicpgx.org/guidelines/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6789586/

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PharmGKB

- PharmGKB is an NIH-funded resource that provides information about how human genetic variation affects response to medications.
- PharmGKB collects, curates and disseminates knowledge about clinically actionable gene-drug associations and genotype-phenotype relationships.

www.pharmgkb.com

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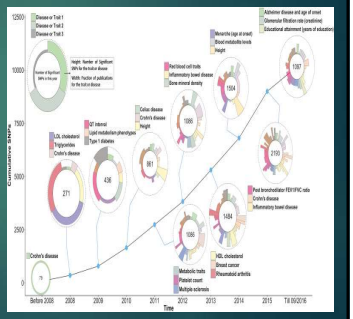
Genome-Wide Association Studies (GWAS)

- A research approach used to identify genomic variants that are statistically associated with a risk for a disease or a particular trait
- This method studies the entire set of DNA (the genome) of a large group of people, searching for small variations, called single nucleotide polymorphisms or SNPs (pronounced "snips")

https://www.cell.com/ajhg/fulltext/S0002-9297(17)30240-9



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Medication Classes That Been Studied for PGX Principles

- Warfarin
- Anesthetics
- Muscle relaxants
- Antiarrhythmics
- Beta Blockers
- Statins
- Antifungals
- Hormonal Contraceptives
- Psychotropic Medications
- Anticonvulsants

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6789586/

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Scope of the Problem in Psychiatry

- Before a patient sees a psychiatrist, it is estimated that 2.9 psychotropic medications fail and it takes an average of 34 months to identify the right medications.
- It is estimated that 30% of patients receiving a psychotropic medication has significant gene-drug interactions. (Patient Medco Study)

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FDA-Approved Psychotropic Drugs with Pharmacogenomic Labeling

Psychotropic	Medication
Antidepressants	Citalopram, Clomipramine, Doxepin, Desipramine, Fluoxetine, Fluvoxamine, Imipramine, Nefazodone, Nortriptyline, Paroxetine, Protriptyline, Trimipramine, Venlafaxine
Antipsychotics	Aripiprazole, Clozapine, Iloperidone, Pimozide, Risperidone, Thioridazine
Anxiolytics/Sedative Hypnotics	Clobazam, Diazepam
Anticonvulsants	Carbamazepine, Valproic Acid
Miscellaneous	Atomoxetine, Modafanil

16

Background

- Diagnosis of psychiatric disorders is variable and subjective
- Psychiatric disorders are inheritable
- Adherence is challenging in psychiatric disorders
- Treatment options for psychiatric disorders can cause medical and life-threatening side and adverse effects

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Knowledge Check:
Why Consider Pharmacogenomics in Psychiatry?

Identify a "limitation" to using the following psychotropics

- Antidepressants
- Antipsychotics
- Anxiolytics
- Anticonvulsants
- Mood stabilizers
- Sedative Hypnotics

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Population Frequency of Cytochrome P450 (CYP) Genotypes

Gene	PM	IM	EM	RM & UM
CYP4502D6	10%	35%	48%	7%
CYP4502C9	2-4%	>35%	~60	N/A
CYP4502C19	2-20%	24-36%	14-44%	30%

**CYP2C19 variability depends on ethnicity*

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Limits with Pharmacogenetic Testing

- High cost
- Long turn around time
- Sensitivity of tests
- Ethical considerations
- Gap in pharmacogenomic literacy

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Pharmacogenomic Practice

In a US study

- Only 1 in 10 physicians (N > 10,000, response rate: 3%) responding reported feeling confident in their knowledge of pharmacogenomics and its clinical application,
- < 1/3 had ever ordered a pharmacogenetic test
- 1/8 had recommended or ordered a test in the previous six months

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6789586

https://pubmed.ncbi.nlm.nih.gov/22278335//

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Question

Heritability contributes to drug response in patients with depression, anxiety, and bipolar disorder.

A. True

B. False

22

Pharmacogenomic Findings in Psychiatry-Depression/Anxiety

- Heritability is approximately 50%
- A low functioning variant of a promotor polymorphism has been identified for the gene coding for the serotonin transporter *HTTLPR* which is a target for the SSRIs.

HTTLPR may predict patients at risk for antidepressant-induced mania

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Pharmacogenomic Findings in Bipolar Disorder

- Hereditary risks range from 10-20% if one parent is bipolar to <70% if both sides of the family have a strong pattern; identical twins don't always develop bipolar disorder

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Pharmacogenomic Findings in Psychiatry- Bipolar Disorder

- Dr. Alexander Niculescu,III, (Indiana University School of Medicine) has identified 10 genes that are related to mood disorders.
- The genes implicated in Bipolar Disorder are found on chromosomes 4,6,12,13,15,16,21, and 22.

25

Pharmacogenomic Findings in Psychiatry- Lithium Response

•There is a linkage to a locus on chromosome 15q in lithium-responsive families with bipolar disorder
Mol. Psychiatry 6(5). 570-578 (2001)

•There is an association of the phospholipase C gene *PLCG1 to lithium-responsive* families with bipolar disorder
Mol. Psychiatry 3(6). 534-538 (1998)
Psychiatr. Genet. 11(1). 41-43 (2001).

26

Pharmacogenomic Findings in Psychiatry-Bipolar Disorder

- The BDNF gene has been implicated in rapid cycling in Bipolar Disorder
- This gene inhibits GSK3beta
- GSKbeta is inhibited by lithium and valproic acid

Hum Mol Genet. 2013 Jun 27. (Epub)

27

Pharmacogenomic Findings in Psychiatry-Antipsychotics

- Clozaril
  - Allele at HLA-DQB1 locus associated with the risk of agranulocytosis
  - Sensitivity of the marker was 21%
    - *J Clin Psych 2011;72:458-463*

28

Pharmacogenomic Findings in Psychiatry-Antipsychotics

- Weight gain may be associated with polymorphisms on the 759 C or T alleles in the 5-HT_{2C} receptor gene (studies involving risperidone, chlorpromazine, and olanzapine)

Lancet 2002;359:2086-2087

Pharmacogenet Genomics 2005;15:195-200

29

Pharmacogenomic Findings in Psychiatry-Response to Antipsychotics

- DRD2 is associated with poor response to antipsychotic drugs, and also increases the liability of weight gain induced by antipsychotics

Pharmacogenet Genomics 2010;20:569-572

30

Impact of ADRs in Treating Epilepsy

•Of those who respond to therapy, ~ 50% will experience an adverse drug effect

• Treatment discontinuation in ~ 25% of patients

• Substantial burden on costs of health care

• Major cause of morbidity and mortality

Perucca & Gilliam. Lancet Neurol 11:792-801; 2012
Schmidt & Schachter. BMJ 348; 2014

31

Challenges in Pharmacotherapy for Epilepsy

- Significant number of patients fail primary drug therapy
- Reasons for treatment failure
  – Adverse drug effects
  – Pharmacoresistance

Pati & Alexopoulos. CCJM 77(7):457-67; 2010
Schmidt & Schachter. BMJ 348; 2014

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Pharmacoresistance

- "failure to control seizures despite a trial of two or three drugs that are suitable for the type of epilepsy and have been appropriately prescribed at maximum tolerated doses" – Pati & Alexopoulos

• Affects ~ 30% of population

Pati & Alexopoulos. CCJM 77(7):457-67; 2010

33

Pharmacoresistance Hypotheses

- **Intrinsic Severity Hypothesis**
  – Response related to disease severity

- **Transporter Hypothesis**
  – Transporters reduce drug concentration

- **Target Hypothesis**
  – Alteration in drug target (receptor)

Pohlmann-eden et al. Epilepsia 54 (Suppl. 2):1-4; 2013

34

Epilepsy Pharmacotherapy: Personalizing Treatment

- Select a drug(s) that fully control seizures, is well tolerated (low risk adverse effects), and is easy for clinicians to prescribe and patients to take

- 25 drugs available to treat epilepsy, which drug is best for your patient?

- Both adverse drug events and pharmacoresistance have a genetic component

– Potential for pharmacogenomics to help guide drug selection

Schmidt & Schachter. BMJ 348; 2014

35

Pull up the package inserts for the following medications:

- Carbamazepine
- Valproic Acid
- Phenytoin
- Lamotrigine
- Oxcarbazepine
- Ezlicarbazepine

- Look at Boxed Warnings and look for any Pharmacogenetic labeling

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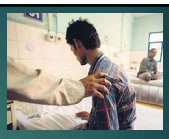
Case



- 26-year-old male admitted to psychiatric department for acute schizophrenic agitation department for acute schizophrenic agitation
- CBZ (200mg bid) was prescribed; 4 days later he developed erythematous papules bullae, and skin erosions
- After transfer to burn center, temp rose to 39.8°C, BP 160/100, HR 124 bpm
- Erosions progressed to include entire buccal mucosa, tongue, & lips; > 90% BSA involved

J Formos Med Assoc. 2007;106:1032-7

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Case Cont'd

- Skin biopsy revealed total epidermal destruction and perivascular lymphocyte infiltration; diagnosis of TEN was made
- After information provided to national database regarding drug database regarding drug-related skin events, related skin events, information about a past CBZ-related SJS episode was obtained
- Therapy with IV hydrocortisone started. The patient developed respiratory distress due to pulmonary edema and died from multi-organ failure 5 days after

J Formos Med Assoc. 2007;106:1032-7

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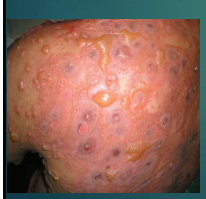
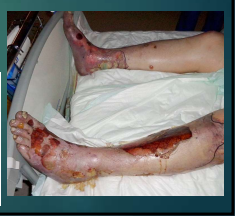
Drug-Mediated Immune Response Cutaneous Reactions- Toxic Epidermal Necrolysis

- Mortality 30%
- Can overlap with SJS when >30% of body surface area is involved





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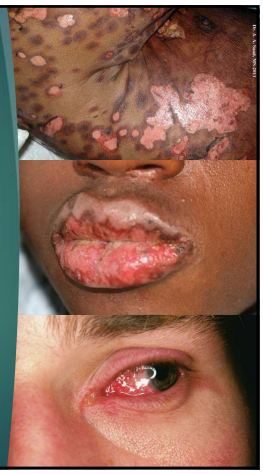
Drug-Mediated Immune Response Cutaneous Reactions- Steven Johnson's Syndrome

- Mortality 30%



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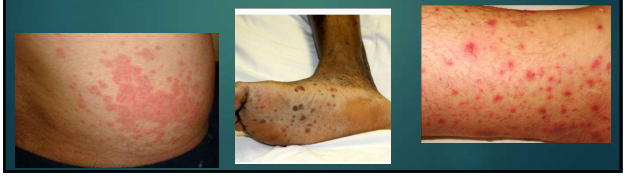
Drug-Mediated Immune Response Cutaneous Reactions- Maculopapular Exanthema

- Usually resolves with drug discontinuation



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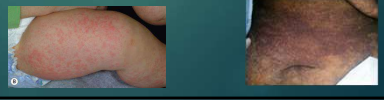
Drug-Mediated Immune Response Cutaneous Reactions – Drug Hypersensitivity Syndrome (DRESS)

- Rash, possible nephritis
- Usually occurs 2-8 weeks after starting medication
- May be accompanied by fever, adenopathy, and other systemic lesions
- Eosinophilia is common
- Responds to systemic steroids

– Mortality 10%



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Case Revisited

- Was it the carbamazepine that caused the problem?

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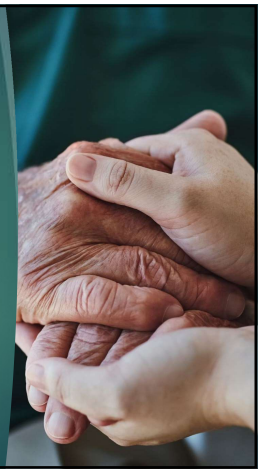
HLA-B Gene

- *Studies ... have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene.*
- *HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia.*
- *Patients with ancestry in genetically at risk populations should be screened for the presence of HLAB*1502 prior to initiating treatment with Tegretol.*



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HLA-B*1502 Identifies Patients at High-Risk for CBZ-SJS/TEN

•

6/6 patients with AED-SJS/TEN positive for HLA-B*1502 ... 4=CBZ, 1=PHT, 1=LTG

Man et al. Epilepsia 2007;48:1015-8 •

- Only 4/12 patients with CBZ-SJS/TEN positive for HLA-B*1502 • – All 4 with Asian ancestry

Lonjou et al. Pharmacogenomics J 2006;6:265-8.

Chung et al. Nature 2004;428:486. Hung et al. Pharmacogenet Genomics 2006;16:297-306

45

Carbamazepine and HLA-B*15:02

- Those positive for HLA-B*15:02 ~ 100-fold more likely to develop carbamazepine-induced SJS/TEN

- Negative predictive value ~100%
- Positive predictive value 1.8-7.7%

– Assumption CBZ-induced SJS/TEN frequency is ~0.25%

– HLA-B*15:02 allele frequency 5-15%

Yip et al. Clin Pharmacol Thera. 92(6); 757-65, 2012

46

Other HLA Genetic Variants Associated with Carbamazepine-Induced Hypersensitivity Reactions

- Significant association between HLA-B*31:01 genotype and carbamazepine induced hypersensitivity reactions
- HLA-A*31:01 observed in more diverse populations
- FDA states "The risks and benefits of Tegretol therapy should be weighed before considering Tegretol in patients known to be positive for HLA-A*3101"

Nihara et al. J Dermatology. 39. 2010
Yip et al. Clin Pharmacol Ther. 92. 2012
McCormack et al. NEJM. 364. 2011
Kim et al. Epilepsy Res. 97. 2011
Hung et al., Pharmacogenet Genomics. 16. 2006
Kashiwagi et al. J Dermatology. 35. 2008
Ozeiu et al. Hum Mol Genet. 20. 2011
Middleton et al. Hum Immunol. 61. 2000

47

Carriers of HLA-B*1502 Allele Beware:

- No other diseases have been linked to HLA-B*1502

Reports linking the HLA-B*1502 allele to SJS/TEN

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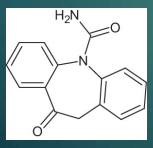
Oxcarbazepine: Cases of SJS/TEN

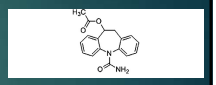
- Pro-drug of 10-monohydrate derivative
- Active component of CBZ
- No carbamazepine 10,11 epoxide



- Shankarkumar, U., et al. Epilepsia 50, 2009
- Chen, Y.C., et al. J Eur Acad Dermatol Venereol 23 (7), 2009
- Hu, F.Y., et al. Seizure 20, 2011
- Leckband et al. Clin Pharmacol Thera. 94 2013
- Oxcarbazepine FDA drug insert

49

Carriers of HLA-B*1502 Allele Beware:



- Eslicarbazepine acetate

Prodrug which is activated to eslicarbazepine (active metabolite to OXC)

*No cases of SJS/TEN ..yet!

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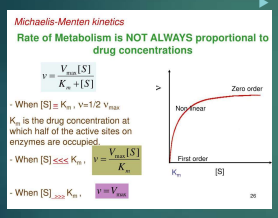
Phenytoin

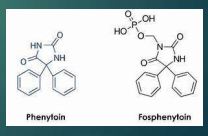


- IV PHT formulation contains propylene glycol

not in fosphenytoin

PHT : <50mg/min

FosPHT: <150/min



51

Potential risk of SJS/TENS with Phenytoin and FosPHT

Hung et al. Pharmacogenomics, 11(3), 2010
•Man et al. Epilepsia, 48(5), 2007
•Neuman et al. Transl Res., 159(5), 2012
•Cheung et al. Epilepsia, 2013
•Locharernkul et al. Epilepsia, 49(12), 2008
•Min et al. Epilepsy Behav., 20(2), 2011
•Leckband, et al. Clin Pharmacol Ther. 94, 2013
•FDA drug insert
HLA-B*15:02 associated with phenytoin induced SJS/TEN

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Lamotrigine

- Associated with SJS/TEN (esp. with rapid dose escalation or used with VPA) Conflicting data
- Dosage alterations with valproic acid derivatives (VPA)
  - Inhibits glucuronidation

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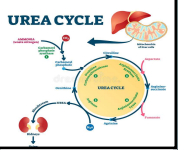
Excerpt from the valproic acid (Depakene) drug label

- "Valproic acid is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency."



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Recommendations for Valproic Acid Urea Cycle Disorders

- Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients:

1)those with a history of unexplained encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;

2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), or protein avoidance;

3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);

4) those with other signs or symptoms of UCD

55

Excerpt from the valproic acid (Depakene) drug label regarding POLG

"POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8796686/

56

A patient was diagnosed with Steven Johnson's Syndrome/Toxic Epidermal Necrolysis after imitating an anticonvulsant. Which allele is most associated with causing this problem?

A. HLA-A*31.01
B. HLA-B*31.01
C. HLA-B*15.01
D. HLA-A*20.01

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Future Use of Pharmacogenomics

- May decrease costs of drug discovery
- May provide more insight on pre-marketing clinical efficacy
- May improve clinical outcomes in clinical practice
  - https://pubmed.ncbi.nlm.nih.gov/36707729/
- GWAS Studies being used more for repurposing drugs
  - https://www.nature.com/articles/s41576-021-00387-z

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Barriers That Still Need to Be Addressed

- Cost of testing
- Access
- Timing
- Reimbursement policies
- Fragmented and lack of portability of EHRs
- PGX literacy gap

https://bit.ly/3EhtDGD
https://blogs.cdc.gov/genomics/2023/05/08/cost-effectiveness/

60

What is currently being done by pharmacists?

- Sequencing
- DNA Extraction
- Algorithms
- Interpretations
- Implementation
- Polymorphisms
- Bioinformatics
- Data security
- Monitoring
- Standardizing recommendations

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Learning Assessment Questions Review

62

Which of the following best describes pharmacoresistance? Select all that apply.

A. Response to a medication is influenced by the severity of the seizures
B. Response to medication based on a patient's co-morbid conditions
C. Response to a medication is due to reduced metabolic transporter
D. Response to a medication based on alterations in drug receptors

63

Which of the following provides guidance to clinicians on how to properly dose medications based on pharmacogenomic characteristics of medications?

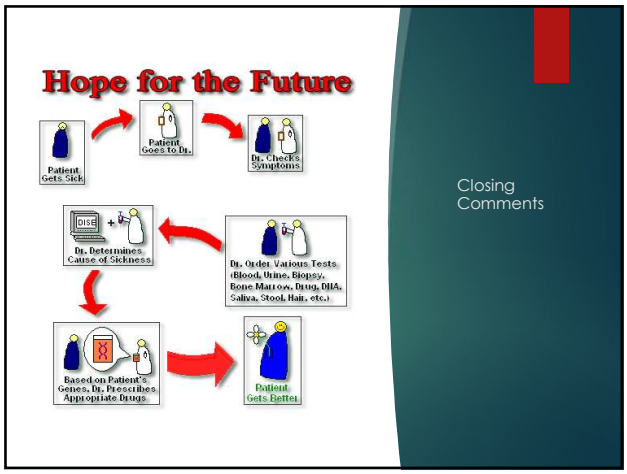
A. GWAS
B. PharmGKB
C. CIPC Guidelines
D. Choices A & B
E. Choices B & C

64

Variants in the CYP2C19 gene can result in altered response to phenobarbital, _____and desmethylclobazam.

A. Phenytoin
B. Valproic acid
C. Zonisamide
D. Lamotrigine

65



Closing Comments

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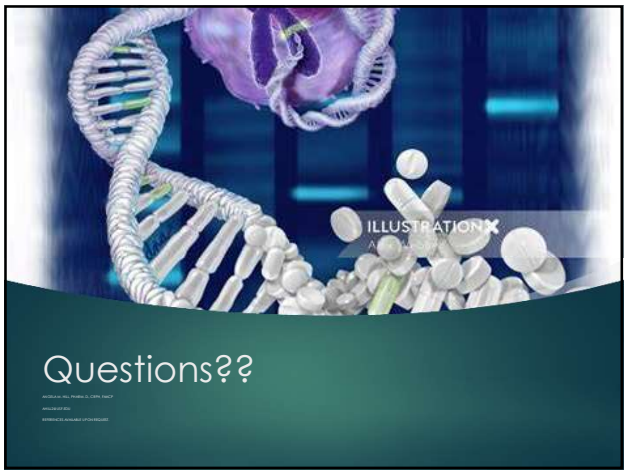

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